Table 2. Prevalence Estimates, Differences, and Ratios of Structural Birth Defects Associated With Receipt of Tdap During Pregnancy, 2007-2013

	Prevalence (Rate per 10 000 Live Births) (N = 324 463)[a]		Prevalence Difference per 10 000 Live Births (95% CI)		Prevalence Ratio (95% CI)	
	Tdap Unexposed	Tdap Exposed	Unadjusted	Adjusted[b]	Unadjusted	Adjusted[b]
Tdap During Any Pregnancy Week						
No. of participants	282 809	41 654				
Any structural birth defect	17 422 (616)	2816 (676)	60 (34 to 86)	−13 (−41 to 15)	1.09 (1.05 to 1.14)	0.98 (0.94 to 1.03)
Selected birth defects[c]	4521 (160)	717 (172)	12 (−1 to 26)	10 (−4 to 25)	1.08 (1.00 to 1.17)	1.06 (0.98 to 1.16)
Microcephaly	348 (12)	38 (9)	−3 (−6 to 0)	−1 (−4 to 2)	0.74 (0.53 to 1.04)	0.86 (0.60 to 1.24)
Tdap During First Trimester (<14 wk Gestation)						
No. of participants	282 809	3321				
Any structural birth defect	17 422 (616)	208 (626)	10 (−73 to 93)	−51 (−132 to 30)	1.02 (0.89 to 1.17)	0.94 (0.82 to 1.07)
Selected birth defects[c]	4521 (160)	59 (178)	18 (−27 to 63)	17 (−29 to 62)	1.11 (0.86 to 1.44)	1.10 (0.85 to 1.42)
Microcephaly	348 (12)	4 (12)	0 (−12 to 12)	−1 (−12 to 9)	0.98 (0.37 to 2.62)	0.96 (0.36 to 2.58)
Tdap During Recommended Period (27-36 wk Gestation)[c]						
No. of participants	120 097	20 568				
Any structural birth defect	8367 (697)	1435 (698)	1 (−37 to 39)	14 (−25 to 53)	1.00 (0.95 to 1.06)	1.02 (0.96 to 1.08)
Selected birth defects[c]	1920 (160)	356 (173)	13 (−6 to 32)	15 (−4 to 35)	1.08 (0.97 to 1.21)	1.09 (0.97 to 1.23)
Microcephaly	146 (12)	21 (10)	−2 (−7 to 3)	−1 (−5 to 4)	0.84 (0.53 to 1.33)	1.01 (0.63 to 1.61)

Abbreviation: Tdap, tetanus, diphtheria, and acellular pertussis.

[a] Pregnancy cohort was limited to 2010-2013 for California sites and to 2012-2013 for other sites in Minnesota, Colorado, Oregon, Washington, and Wisconsin.

[b] Adjusted for propensity score including maternal age at delivery, race/ethnicity, pregnancy delivery year, Kotelchuck Adequacy of Prenatal Care Utilization Index, hospitalization at less than 20 weeks' gestation, maternal smoking, preexisting hypertension, preexisting pulmonary, heart, or renal conditions, site, and mean census tract poverty level.

[c] Diagnostic codes for selected major structural birth defects: spina bifida (741.0x and 741.9x); encephalocele, cranial meningocele, or encephalomyelocele (742.0); microcephalus (742.1); holoprosencephaly (742.2); anophthalmia or microphthalmia (743.00 and 743.10-743.12); cataracts and other lens defects (743.2x and 743.30-743.36); anotia or microtia (744.01 and 744.23); severe congenital heart disease: single ventricle, tricuspid atresia, Ebstein anomaly, hypoplastic left heart, hypoplastic right heart, common truncus, transposition, atrioventricular septal defects, tetralogy of Fallot, aortic valve atresia or stenosis, coarctation, total anomalous pulmonary venous return, and anomalous coronary artery (745.0, 745.1x, 745.2-745.3, 745.6x, 745.7, 746.00, 746.01, 746.1-746.3, 746.7, 746.85,747.1x, 747.22, and 747.41); other congenital heart disease: septal defects, heterotaxy, partial anomalous pulmonary venous return (745.4, 745.8, 745.9, 759.3, and 747.42); choanal atresia (748.0); cleft lip or cleft palate (749.0, 749.00-749.04, 749.1, 749.10-749.14, 749.2, and 749.20-749.25); esophageal atresia with or without tracheoesophageal fistula (750.3); pyloric stenosis (750.5); intestinal atresia or stenosis (751.1 and 751.2); biliary atresia (751.61); second- or third-degree hypospadias, (752.61); renal agenesis or hypoplasia (753.0); renal dysplasia (753.15); congenital hydronephrosis (753.2x); bladder exstrophy (753.5); posterior urethral valve or prune belly (753.60 and 756.71); limb deficiency (755.2-755.9); sacral agenesis (756.13); diaphragmatic hernia (756.6); gastroschisis or omphalocele (756.72, 756.73, and 756.79).

(Group Health Cooperative), for providing subject matter expertise, technical assistance, and review of the study; Leslie Kuckler, MPH, Beth Molitor, MBA, and Avalow Olsen, BS (all from HealthPartners Institute), for their assistance with data collection; and Natalie McCarthy, MPH (CDC), for her assistance with data collection and management and administrative and technical support. Compensation for all contributors was received through the CDC.

1. Centers for Disease Control and Prevention. Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant women. *MMWR Morb Mortal Wkly Rep*. 2013;62(7):131-135.

2. Conselho Regional De Medicina Do Estado Do Paraná. Informe Técnico para Implantação da Vacina Adsorvida Difteria, Tétano e Coqueluche (Pertussis Acelular) Tipo adulto—dTpa [in Spanish]. http://www.crmpr.org.br/uploadAddress/info_dtpa_ministerio-saude-setembro-2014%5B1614%5D.pdf. Accessed September 15, 2016.

3. Keller-Stanislawski B, Englund JA, Kang G, et al. Safety of immunization during pregnancy. *Vaccine*. 2014;32(52):7057-7064.

4. Baggs J, Gee J, Lewis E, et al. The Vaccine Safety Datalink. *Pediatrics*. 2011;127(suppl 1):S45-S53.

5. Naleway AL, Gold R, Kurosky S, et al. Identifying pregnancy episodes, outcomes, and mother-infant pairs in the Vaccine Safety Datalink. *Vaccine*. 2013;31(27):2898-2903.

6. Kharbanda EO, Vazquez-Benitez G, Lipkind HS, et al. Evaluation of the association of maternal pertussis vaccination with obstetric events and birth outcomes. *JAMA*. 2014;312(18):1897-1904.

COMMENT & RESPONSE

Association of a Genetic Risk Score With Body Mass Index

To the Editor Dr Walter and colleagues[1] reported that a polygenic risk score for body mass index (BMI) showed a differential association across different birth cohorts. For people born between 1900 and 1958, the magnitude of association of the risk score with BMI was reduced compared with people born later. They suggested that changes in the environment may modify the effect of genetic variants associated with BMI. This is an intriguing possibility. Obesity is a known risk factor for a number of adverse health outcomes that lead to increased mortality among individuals with high BMI.[2,3]

A genetic variant associated with heaviness of smoking was differentially associated with smoking initiation (ie, ever vs never) in different age groups.[4] Among people younger than 50 years, the smoking-increasing allele was positively associated with smoking initiation, whereas among people 50 years or older, it was negatively associated with smoking initiation. This differential association was attributed to the higher rates

of mortality among smokers carrying the smoking-increasing allele, which would lead to a negative association between genotype and likelihood of ever being a smoker at older ages, when greater differential attrition by genotype has occurred.

Thus another interpretation of the results reported by Walter and colleagues[1] is that the differential association between BMI-related genetic variants and BMI across birth cohorts derives from the causal effects of elevated BMI on mortality. Persons in more recent cohorts were younger when their genetic score and BMI were measured, and therefore the association is unlikely to be affected by survival bias. Persons in less recent cohorts were older when measured, thus excluding those who already died, including through BMI-related mechanisms.[2,3] Some support for this suggestion is found in Table 1 in the article—for age groups at which few people have died, a positive association between age and BMI (reflecting the general tendency of BMI to increase with age) was seen, whereas at older ages there was a negative association.

If BMI is associated with increased mortality, the association between BMI and BMI-related variants will be distorted through collider bias.[5] If BMI-related genetic variants are also associated with increased mortality via mechanisms that do not involve measured BMI, this will bias the observed associations even further. Statistical methods are needed that account for differential attrition and survival bias.

Marcus R. Munafò, PhD
Kate Tilling, PhD
George Davey Smith, MD, DSc

Author Affiliations: MRC Integrative Epidemiology Unit, University of Bristol, Bristol, United Kingdom.

Corresponding Author: Marcus R. Munafò, PhD, School of Experimental Psychology, University of Bristol, Bristol BS8 1TU, United Kingdom (marcus.munafo@bristol.ac.uk).

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

1. Walter S, Mejía-Guevara I, Estrada K, Liu SY, Glymour MM. Association of a genetic risk score with body mass index across different birth cohorts. *JAMA*. 2016;316(1):63-69.

2. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA*. 2013;309(1):71-82.

3. Global BMI Mortality Collaboration. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. *Lancet*. 2016;388(10046):776-786.

4. Taylor AE, Munafò MR; CARTA Consortium. Commentary: does mortality from smoking have implications for future Mendelian randomization studies? *Int J Epidemiol*. 2014;43(5):1483-1486.

5. Cole SR, Platt RW, Schisterman EF, et al. Illustrating bias due to conditioning on a collider. *Int J Epidemiol*. 2010;39(2):417-420.

To the Editor A study by Dr Walter and colleagues[1] found differential associations between a polygenic genetic risk score and BMI across different US birth cohorts. In 2015, we published a study about genetic inheritance and body mass.[2] One of our analyses was basically identical to theirs in which the following hypothesis was tested: "… that the genetic influence on body mass is greater among recent cohorts than among earlier ones," using data from the Health and Retirement Study (HRS).

Our study used 8816 non-Hispanic white participants, whereas the study by Walter and colleagues[1] also included 1306 black participants. Both studies constructed a polygenic score based on a well-known genome-wide association study.[3] Both studies concluded that increased genetic influence on BMI was found in more recent birth cohorts.

Hexuan Liu, MS
Guang Guo, PhD

Author Affiliations: School of Criminal Justice, University of Cincinnati, Cincinnati, Ohio (Liu); Department of Sociology, University of North Carolina, Chapel Hill (Guo).

Corresponding Author: Hexuan Liu, MS, University of Cincinnati, CECH, School of Criminal Justice, 2610 McMicken Circle, 660 Dyer Hall, PO Box 210389, Cincinnati, OH 45221 (hexuan.liu@uc.edu).

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

1. Walter S, Mejía-Guevara I, Estrada K, Liu SY, Glymour MM. Association of a genetic risk score with body mass index across different birth cohorts. *JAMA*. 2016;316(1):63-69.

2. Liu H, Guo G. Lifetime socioeconomic status, historical context, and genetic inheritance in shaping body mass in middle and late adulthood. *Am Sociol Rev*. 2015;80(4):705-737.

3. Speliotes EK, Willer CJ, Berndt SI, et al; MAGIC; Procardis Consortium. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat Genet*. 2010;42(11):937-948.

In Reply Dr Munafò and colleagues suggest that survival bias may account for our findings of attenuated associations between genotype and phenotype among cohorts born earlier in the century.[1] Although we agree this is mathematically possible, the magnitude of influence of selective survival in our study was probably minimal. Unlike the age-stratified analyses reported by Taylor and Munafò,[1] our analyses relied on a mixed model estimated in data with successive enrollments of more recent birth cohorts. Because of the HRS design, we were able to control for age, and we estimated genotype-phenotype associations for members of different birth cohorts at the same age (65 years for white participants). This eliminates most of the potential for survival bias, but a bias could still occur under 2 causal structures. In one scenario (in which genotype influences BMI and both BMI and cohort influence survival, so that among survivors the genotype-BMI association is altered), the magnitude of this bias would depend on the differential survival to the same age of different birth cohorts, and whether that differential was due to BMI.

For example, 63% of white individuals born in 1940 survived to age 65 years, whereas only 52% of white individuals born in 1920 survived to age 65 years.[2] This survival differential is unlikely to be due to BMI, however, given that nearly all these improvements in survival were achieved by age 35 years, when BMI-related mortality is unusual.[3] In the second scenario (in which both BMI and genotype have direct effects on survival, so survival is a collider between them, as Munafó and colleagues suggest), the magnitude of bias would additionally depend on the direct effect of the genetic risk score for BMI (GRS-BMI) on survival. Although this type of survival bias is plausible, it is small unless the factors have extremely strong and interactive effects on survival.[4,5]

Both scenarios imply that the average GRS-BMI should be lower for study participants in earlier birth cohorts. However, we showed (Table 2 in the article and eTable 1 in the Supplement) that genetic risk remained stable across the birth cohorts, despite major changes in BMI. Furthermore, GRS-BMI did not predict mortality for white participants in HRS (P = .45). Additionally, we estimated a model testing whether the birth year by GRS-BMI interaction differed for white respondents above or below age 65 years and found no evidence of such effect modification by age (P = .24).

With respect to Mr Liu and Dr Guo, upon reviewing their article,[6] we agree that our results for white respondents substantially overlap with theirs. This type of overlap is always a risk with publicly available data sets such as the HRS, but missing their citation was a mistake on our part. Our manuscript was mostly finished prior to their publication (first full draft completed March 2014). We attempted to update our literature review, but we failed to identify this important publication. We apologize for our error. We consider it an indication of the importance of this research question that it was undertaken by multiple independent research groups, and we are pleased that the findings are consistent.

M. Maria Glymour, ScD
Stefan Walter, PhD
Iván Mejía-Guevara, PhD

Author Affiliations: Department of Epidemiology and Biostatistics, University of California, San Francisco (Glymour, Walter); Harvard Center for Population and Development Studies, Harvard University, Cambridge, Massachusetts (Mejía-Guevara).

Corresponding Author: Maria Glymour, ScD, Department of Epidemiology and Biostatistics, University of California, San Francisco, 550 16th St, Mission Hall, Second Floor, San Francisco, CA 94132 (mglymour@psg.ucsf.edu).

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

1. Taylor AE, Munafò MR; CARTA consortium. Commentary: does mortality from smoking have implications for future Mendelian randomization studies? *Int J Epidemiol*. 2014;43(5):1483-1486.

2. Arias E. United States Life Tables, 2011. *Natl Vital Stat Rep*. 2015;64(11):1-63.

3. Schmidt M, Johannesdottir SA, Lemeshow S, et al. Obesity in young men, and individual and combined risks of type 2 diabetes, cardiovascular morbidity and death before 55 years of age: a Danish 33-year follow-up study. *BMJ Open*. 2013;3(4):e002698.

4. Mayeda ER, Tchetgen Tchetgen EJ, Power MC, et al. A simulation platform for quantifying survival bias: an application to research on determinants of cognitive decline. *Am J Epidemiol*. 2016;184(5):378-387.

5. Glymour MM, Vittinghoff E. Commentary: selection bias as an explanation for the obesity paradox: just because it's possible doesn't mean it's plausible. *Epidemiology*. 2014;25(1):4-6.

6. Liu H, Guo G. Lifetime socioeconomic status, historical context, and genetic inheritance in shaping body mass in middle and late adulthood. *Am Sociol Rev*. 2015;80(4):705-737.

Assessing the Patient With Arthralgia, Fevers, and Rash

To the Editor In their JAMA Clinical Challenge article, Dr Ardalan and colleagues[1] described a patient with arthralgia and fevers accompanied by a papulonodular rash, which was diagnosed as erythema nodosum and an adverse reaction to azathioprine. The authors supported their diagnosis by noting that similar cases have been reported and that the clinical and laboratory findings were consistent with the diagnosis.

We have some skepticism about the diagnosis of erythema nodosum and believe neutrophilic dermatosis should be considered. Erythema nodosum is a type IV hypersensitivity reaction–mediated condition characterized by granulomatous tissue on skin biopsy. Neutrophilic dermatosis is a group of skin lesions often described in the context of adverse drug reactions, characterized by neutrophilic invasion of the dermal tissue, in which no granulomatous tissue is observed on biopsy.[2] Deposition of small immunocomplexes in the endothelium of small vessels (type III hypersensitivity reaction) may trigger a neutrophilic invasion of the vessel wall, leading to stromal aggregation of neutrophilic infiltrates.[3] The authors reported that conventional skin biopsies are often nondiagnostic because both syndromes present with the same histological image of neutrophil invasion of the stromal tissue. However, we believe that immunohistochemical assessment of a skin biopsy sample to detect granulomas should have been performed to differentiate the possible diagnoses of the patient's skin lesions. Furthermore, the presence of granulomas would confirm the association of the dermal lesions with autoimmune hepatitis (a type II and IV hypersensitivity reaction–mediated disease), whereas absence of granulomatous tissue would indicate an adverse reaction to azathioprine administration (a type III hypersensitivity reaction–mediated condition).

Neutrophilic dermatosis is the most common skin adverse reaction associated with azathioprine administration.[4] Moreover, elevated levels of neutrophils in the peripheral blood are more consistent with neutrophilic dermatosis than with erythema nodosum. Therefore, we believe that this particular patient's clinical presentation, consisting of fevers, arthralgia, and skin lesions combined with elevated neutrophil levels in peripheral blood, is more consistent with neutrophilic dermatosis than with erythema nodosum. Immunohistochemical assessment of a skin biopsy sample would provide a definite diagnosis of the specific lesions.

Alexandros Sarantopoulos, MD, PhD
Ioannis Gkougkourelas, MD, PhD
Panagiota Boura, MD, PhD

Author Affiliations: Second Department of Internal Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece.

Corresponding Author: Alexandros Sarantopoulos, MD, PhD, Clinical Immunology Unit, Second Department of Internal Medicine, Aristotle University of Thessaloniki, Hippokration General Hospital, 49 Konstantinoupoleos str, Thessaloniki 54642, Greece (alexsar@med.auth.gr).

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

1. Ardalan ZS, Vasudevan A, Testro AG. Arthralgia and fevers in a patient with autoimmune hepatitis. *JAMA*. 2016;316(1):91-92.

2. Corazza M, Lauriola MM, Borghi A, Marzola A, Virgili A. Sweet's syndrome: a retrospective clinical, histopathological and immunohistochemical analysis of 11 cases. *Acta Derm Venereol*. 2008;88(6):601-606.

3. Cyrus N, Stavert R, Mason AR, Ko CJ, Choi JN. Neutrophilic dermatosis after azathioprine exposure. *JAMA Dermatol*. 2013;149(5):592-597.

4. Bidinger JJ, Sky K, Battafarano DF, Henning JS. The cutaneous and systemic manifestations of azathioprine hypersensitivity syndrome. *J Am Acad Dermatol*. 2011;65(1):184-191.